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Original article

Effect of maternal lifestyle intervention on metabolic health and adiposity of offspring: Findings from the Finnish Gestational Diabetes Prevention Study (RADIEL)

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ABSTRACT

Aim. – To assess in women at high risk of gestational diabetes mellitus (GDM) the effect of a lifestyle intervention on the metabolic health of their offspring around 5 years after delivery.
Methods. – For the original Finnish gestational diabetes prevention study (RADIEL), 720 women with a prepregnancy body mass index (BMI) $\geq$ 30 kg/m^2 and/or previous GDM were enrolled before or during early pregnancy and allocated to either an interventional (n = 126) or conventional (n = 133) care group. The present 5-year follow-up substudy assessed the metabolic health outcomes of their offspring. Age- and gender-standardized residuals of metabolic health components (waist circumference, mean arterial pressure, high-density lipoprotein and triglyceride levels, and fasting insulin/glucose ratio) were also combined to determine the accumulation of metabolic effects. Body composition was assessed by electrical bioimpedance.
Results. – Offspring of women in the intervention group had a less optimal metabolic profile after the 5-year follow-up compared with offspring in the usual care group (P = 0.014). This difference in metabolic health was primarily related to lipid metabolism, and was more prominent among boys (P = 0.001) than girls (P = 0.74). Neither GDM, gestational weight gain, prepregnancy BMI, offspring age nor timing of randomization (before or during pregnancy) could explain the detected difference, which was also more pronounced among the offspring of GDM pregnancies (P = 0.010). Offspring body composition was similar in both groups ($P > 0.05$).
Conclusion. – The lifestyle intervention aimed at GDM prevention was associated with unfavourable metabolic outcomes among offspring at around 5 years of age.

Introduction

The global rate of increase in obesity prevalence is now too high to be explained solely by sedentary behaviours, unhealthy diets or direct genetic factors [1]. For several years, the theory of developmental programming has provided an additional explanation for the trend. According to the Developmental origins of health and disease (DOHaD) hypothesis, the association of unfavourable intrauterine conditions related to, for example, maternal adiposity [2], excessive gestational weight gain [3] and/or gestational diabetes mellitus (GDM) [2,4] with adverse offspring outcomes

Abbreviations: ADA, American Diabetes Association; ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; MAP, mean arterial pressure; MetS, metabolic syndrome; OGTT, oral glucose tolerance test; SD, standard deviation; TG, triglycerides; WC, waist circumference.

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can be at least partly explained by epigenetic mechanisms such as DNA methylation and histone modifications [5]. However, the question remains as to whether this information is of any use in addressing the epidemic. Also, as the fetal environment is possibly modifiable, lifestyle interventions before and during pregnancy may be able to alter offspring health trajectories.

Many lifestyle interventions during pregnancy focused on the reduction of GDM and its adverse outcomes have been conducted but, in general, the results have been inconclusive [6–8]. To a large extent, the effects of such interventions have been assessed through health parameters in women and their offspring either during pregnancy or the neonatal period. Only a few studies have assessed the effect of GDM preventative interventions on health parameters in the offspring beyond the neonatal period [9], and very few for > 1 year [10].

As the number of hard endpoints in childhood is extremely small, intermediate outcomes and surrogate markers are generally used to assess paediatric health trajectories. Many have even tried to define a paediatric clustering of risk factors equivalent to adult metabolic syndrome (MetS). Although it is generally accepted that the key components of paediatric MetS are abdominal obesity, elevated fasting glucose, insulin resistance, abnormal lipid profile and high blood pressure, establishing a clear-cut definition has proved difficult. Thus, a number of different definitions of paediatric MetS have been proposed, but met with a lack of consensus as to which one to use. Furthermore, paediatric MetS displays major instability from childhood to adolescence and adulthood and therefore lacks reliable predictive value regardless of the definition used [11]. Nevertheless, clusters of metabolic abnormalities in childhood do arise, with the prevalence of paediatric MetS reaching 3–39%, depending on the population assessed and defining criteria applied [12,13]. In addition, the association of childhood metabolic abnormalities with adult health risk factors is well established [14,15].

Thus, the present study was designed to assess paediatric metabolic health by analyzing its generally accepted key components both separately and together as a calculated average, based on previous publications [16–19]. In particular, the purpose of this study was to assess the effect of a maternal lifestyle intervention aiming to reduce the development of GDM in high-risk women before, during and after pregnancy on the metabolic health of the offspring at around 5 years after delivery.

Material and methods

Study design

This was a secondary analysis and follow-up study of women and their offspring participating in the Finnish gestational diabetes prevention study (RADIEL), a prospective cohort study conducted in the cities of Helsinki and Lappeenranta between 2013 and 2017. The original RADIEL (2008–2014) was a lifestyle interventional trial aiming to reduce GDM development in high-risk women at three maternity hospitals in the Helsinki metropolitan area (Helsinki University Hospital, Kätilöopisto Maternity Hospital, Jorvi Hospital) and at the South Karelia Central Hospital in Lappeenranta [20]. A total of 720 women were recruited before or during early pregnancy and randomized to either an interventional or conventional (control) study group. The intervention was based on structured counselling on physical activity and diet during visits.

The study protocol included visits to a study nurse every trimester during pregnancy, as well as at 6 weeks, 6 months and 12 months after delivery, for all participants. In addition, the women who were enrolled before pregnancy visited the study nurse every 3 months until pregnancy. At each study visit, the participants filled in questionnaires, underwent physical examination including anthropometric and blood pressure measurements, and had blood samples taken.

In addition to the study protocol, participants in both study arms received antenatal healthcare provided by the public healthcare system, according to Finnish standard practice. At the time of the trial, conventional care during pregnancy consisted of 10–15 visits to a nurse and two or three appointments with a physician.

Intervention group

During visits by women in the intervention group, trained study nurses and nutritionists gave them structured counselling on exercise and diet. Those enrolled in the prepregnancy period with a prepregnancy body mass index (BMI) $\geq$ 25 kg/m^2 were recommended to lose 5–10% of their body weight prior to conception. Women with a prepregnancy BMI $\geq$ 30 kg/m^2 were recommended to gain no weight during the first two trimesters of pregnancy.

Advice on diet was given according to the Finnish national nutrition guidelines and Nordic Nutrition Recommendations [21,22]. To achieve their goals, women in the intervention group were advised to increase their intake of vegetables, legumes, fruits, berries, fibre and wholegrain products, vegetable fats and low-fat dairy, and to avoid sugar-rich foods. Also, structured counselling was offered to each individual participant by study nurses. Additional dietary advice was given only at the time of enrolment by a nutritionist during a 2-h session in groups of 6–8 participants.

The goal of the physical-activity intervention was to achieve at least 150 min/week of exercise at moderate intensity. This was defined as any form of physical activity during which the participant becomes slightly out of breath and is sweating, but is still able to talk. In addition, all of the women were encouraged to promote exercise during their daily commutes and/or in conjunction with everyday household tasks, and to maintain physically active lifestyles. To this end, the participants were offered free guided-exercise sessions once a week and free entry tickets to public swimming facilities. Moreover, each participant had to devise an individual exercise plan assisted by the study nurse during the first study visit. This plan was then modified if necessary during subsequent visits.

Control group

Study visits by participants in the conventional care (control) group followed the same time schedule as the intervention group, and their visits usually lasted half an hour. At the first visit, these women received information leaflets on diet and exercise during pregnancy similar to those provided at maternity clinics.

The methodological details of the original RADIEL have been published previously elsewhere [20]. Every participant entered the RADIEL voluntarily and gave their informed consent to participate. The study complied with the Declaration of Helsinki and received approval by the ethics committees of Helsinki University Hospital (14 September 2006, Dnro 300/E9/06) and South Karelia Central Hospital (11 September 2008, Dnro M06/08). The RADIEL was registered at ClinicalTrials.gov (IDr: NCT01698385).

Participants

For the original RADIEL, women with a history of GDM and/or a prepregnancy BMI $\geq$ 30 kg/m^2 were recruited while either planning a pregnancy or during early pregnancy ($< 20 \pm 0$ weeks of gestation). Exclusion criteria were age < 18 years, multiple pregnancy, diabetes diagnosed before pregnancy, use of regular medication affecting glucose metabolism, physical disability, severe psychiatric disorder, current substance abuse and difficulty cooperating due to inadequate language skills.

Participants with a viable singleton pregnancy and at least one study visit during pregnancy were eligible for an invitation to the 5-year follow-up substudy including their offspring (n = 607). Of these, 595 mother–child dyads were approached, resulting in a total of 332 dyads attending the follow-up visit 4–7 years after delivery. On analyzing offspring metabolic health parameters, children lacking more than one of the components used to assess metabolic health were excluded, leaving a final total number of 263 participating dyads (Fig. 1).

Measurements

The follow-up study visit included blood sampling, and anthropometric and blood pressure measurements. Blood was drawn after approximately 4 h of fasting. Methods used for the laboratory analyses have been previously published elsewhere [23]. Duplicate waist-circumference (WC) measurements were taken in the horizontal plane midway between the lowest rib and iliac crest to the nearest 0.1 cm. Triplicate blood pressure measurements of the right arm were taken in sitting position with a sphygmomanometer (Intellisense M6 W, Omron Corporation, Kyoto, Japan). Mean arterial pressure (MAP) was calculated using the formula MAP = diastolic blood pressure + (systolic blood pressure–diastolic blood pressure) × 1/3. BMI-for-age Z-scores were calculated according to World Health Organization (WHO) recommendations [24]. To assess body composition, a multifrequency electrical bioimpedance measurement method was used (InBody 720/InBody 3.0, Biospace Co., Ltd, Seoul, Korea).

GDM was diagnosed according to national recommendations at the time, using one or more pathological glucose values based on the threshold levels recommended by the American Diabetes Association (ADA) in 2008: fasting plasma glucose (FPG) ≥ 5.3 mmol/L; 1-h glucose ≥ 10.0 mmol/L; and 2-h glucose ≥ 8.6 mmol/L [25]. All women also underwent a 75-g 2-h oral glucose tolerance test (OGTT) at 12–16 weeks of gestation. In cases of normal results, the OGTT was repeated at 24–28 weeks of gestation unless treatment for GDM had been initiated. The 75-g 2-h OGTT is the standard diagnostic test for GDM in Finland and similar to the ADA one-step strategy, but different from the ADA two-step strategy, which uses a 100-g OGTT [26]. After a diagnosis of GDM, lifestyle management was initiated. Pharmacological treatment was added in cases where FPG levels were repeatedly > 5.5 mmol/L or > 7.8 mmol/L at 1 h postprandially [27]. Gestational weight gain was estimated by calculating the difference between weight during the third trimester [measured during the study visit at 35.1 ± 1.1 standard deviation (SD) weeks of pregnancy or, in cases of participants not attending the study visit, at the corresponding visit to an antenatal clinic] and the self-reported prepregnancy weight or weight measured at the last study visit prior to pregnancy. Data on alcohol consumption, smoking and education levels (in years) were self-reported.

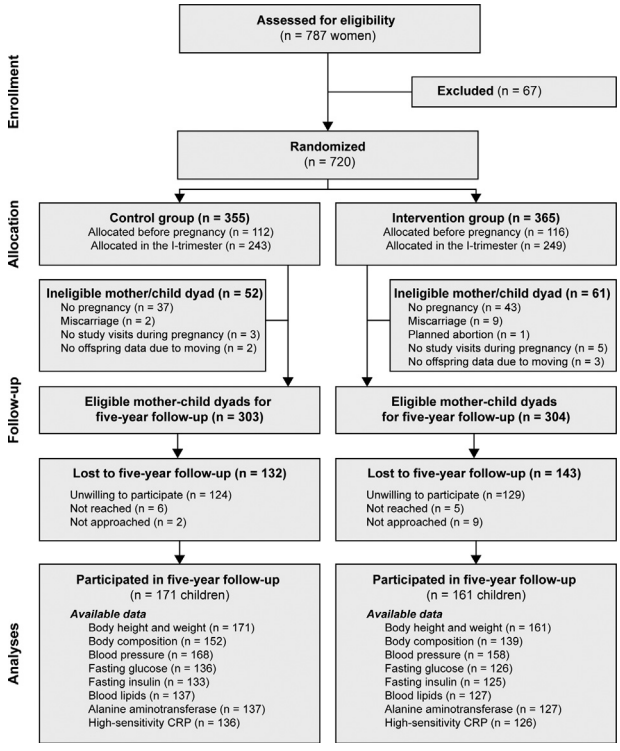

Fig. 1. Flow chart of the present substudy.

Outcomes

The main outcome investigated in this substudy was offspring metabolic health, as assessed through the total metabolic parameter comprising age- and gender-standardized residuals of WC, MAP, fasting insulin/glucose ratio, and inverted high-density lipoprotein (HDL) cholesterol (1/HDL) and triglyceride (TG) concentrations. Secondary outcomes were body fat mass and body fat percentages in the offspring.

Statistics

Data are presented as means ± SD with 95% confidence intervals (CI), as medians with interquartile range (IQR) or as numbers with percentages. Also, for this substudy, it was decided to use data obtained during the first-trimester visit as baseline for all participants. Unpaired t and chi-squared tests were used to compare baseline characteristics between the two study groups (intervention vs. controls) as well as those included or lost to the 5-year follow-up. For measurements of WC, MAP, fasting insulin/glucose ratio, 1/HDL cholesterol, TG, alanine aminotransferase (ALT) and high-sensitivity C-reactive protein (hs-CRP), linear regression analyses were first applied to calculate the age- and gender-standardized residuals of the study population. Then, to assess the accumulation of metabolic health parameters within each given individual, the means of standardized WC, MAP, fasting insulin/glucose ratio, 1/HDL cholesterol and TG were also calculated. These variables were chosen to comprise the total metabolic parameter based on previous published research [16–19]. An unpaired t test was also applied to compare offspring metabolic health parameters, ALT, hs-CRP and body composition between intervention and control mothers. In cases of violations of assumptions (non-normality), a bootstrap-type test was applied. For sensitivity analyses, stratified primary outcome (total metabolic health) analyses were performed according to offspring gender, randomization timing (before pregnancy vs. early pregnancy) and GDM presence or absence during the index pregnancy. Moreover, linear regression analyses were used to adjust the primary analyses with possible covariates [prepregnancy BMI, homoeostasis model assessment of insulin resistance (HOMA-IR) at baseline, recruitment time point, intervention group, number of previous children]. $P < 0.05$ was set as the threshold for statistical significance, and all analyses were performed with Stata/SE version 14.2 and 15.1 software (StataCorp, College Station, TX, USA).

Results

Maternal characteristics

At the first trimester visit, there were no differences in maternal demographic data or clinical characteristics between the two study groups (Table 1). However, differences in these baseline data were

Table 1
First-trimester maternal demographic and clinical characteristics by interventional or conventional care (control) group.

Characteristics	Control (n = 137)	Intervention (n = 126)	P
Randomization before pregnancy	34 [25]	38 [30]	0.33
Gestational age (weeks)	13 (1.7)	13 (2.0)	0.60
Age (years)	33 (5)	33 (4)	0.54
Prepregnancy			
Body weight (kg)	84 (17)	86 (18)	0.67
Body mass index (kg/m^2)	30.7 (5.6)	30.9 (6.0)	0.82
Education level (years)	14 (2.2)	14 (1.9)	0.93
Previous children			0.52
None	42 [31]	31 [25]	
1	64 [47]	62 [49]	
2+	31 [23]	33 [26]	
Previous GDM	69 [50]	69 [55]	0.33
Blood pressure (mmHg)			
Systolic	119 (13)	121 (12)	0.17
Diastolic	77 (9)	76 (9)	0.94
Total cholesterol (mmol/L)	4.8 (0.9)	4.9 (0.9)	0.08
HDL cholesterol (mmol/L)	1.6 (0.3)	1.7 (0.3)	0.19
Total triglycerides (mmol/L)	1.3 (0.5)	1.3 (0.5)	0.31
Fasting glucose (mmol/L)	5.1 (0.4)	5.0 (0.4)	0.71
Insulin (mU/L)	8.4 (5.4)	8.4 (5.1)	0.99
HOMA-IR	1.8 (1.1)	1.9 (1.3)	0.66
Smoking	7 [5]	5 [4]	0.67
Alcohol use	5 [4]	5 [4]	0.92
Dietary index score (points)	10 (3)	11 (3)	0.14
Physical activity (min/week), median (IQR)	60 (30, 120)	75 (30, 140)	0.58
GDM during index pregnancy	67 [49]	60 [48]	0.84
GDM treated with insulin	13 [9.5]	20 [16]	0.12

Data are presented as means (standard deviation, SD) or as numbers [%] unless otherwise stated; GDM: gestational diabetes mellitus; HDL: high-density lipoprotein; HOMA-IR: homoeostasis model assessment of insulin resistance; IQR: interquartile range.

found between the women who attended the 5-year follow-up and those who were lost to follow-up. In the intervention group, the mean age of non-attending mothers was lower by 1.4 years (95% CI: 0.3–2.5; P = 0.01) vs. those attending. In addition, among the non-attenders, the proportion of mothers recruited before pregnancy was significantly lower (14%) than among the attenders (30%; P = 0.001). In the control group, non-attending mothers differed from attending mothers only by having higher mean levels of HDL cholesterol (0.11, 95% CI: 0.02–0.19; P = 0.01).

Overall, the proportion of women who developed GDM in our substudy was 48.5%. In the intervention group, 49.2% were diagnosed with GDM (P = 0.79) vs. 47.6% in the control group. Also, mean gestational weight gain did not differ between these groups (P = 0.79).

Offspring metabolic health parameters

The children attending the follow-up visit were aged 4–7 years (mean age: 5.1 ± 0.5 years). An association was detected between the intervention and offspring metabolic health, with more unfavourable metabolic components observed in the offspring of women in the intervention group (Fig. 2). The mean ± SD value of the total metabolic parameter was 0.09 ± 0.63 in the intervention group and -0.08 ± 0.46 in the controls (P = 0.014). Differences in metabolic component values between the two groups were related to glucose and lipid metabolism and, specifically, to 1/HDL and TG concentrations (Fig. 2). Further analyses also suggested that the association of the intervention with poorer metabolic outcomes was male-specific (Fig. 3): the mean ± SD value among boys from the intervention group was 0.15 ± 0.60, whereas the corresponding value in the control group was −0.13 ± 0.40 (P = 0.001).

Body composition and inflammatory markers

There was no difference between the two study groups regarding offspring body composition and BMI-for-age Z-scores (Table 2). Also, age- and gender-standardized values of ALT did not differ significantly between the groups, with a Z-score of 0.03 ± 1.13 in the intervention group and −0.03 ± 0.87 in the control group (P = 0.60). Likewise, the age- and gender-standardized values of hs-CRP were similar in both groups, with a Z-score of 0.1 ± 1.23 in the intervention group and −0.09 ± 0.73 in the controls (P = 1.14).

Sensitivity analyses

A set of sensitivity analyses related to metabolic health parameters was also performed. First, the offspring were stratified according to maternal GDM status (Fig. 4). Among the offspring of GDM pregnancies, the mean ± SD value of the total metabolic parameter in the intervention group was 0.13 ± 0.58 vs. −0.11 ± 0.43 in the control group (P = 0.01). Among the offspring of non-GDM pregnancies, the tendency was similar but non-significant (P = 0.35). In addition, no significant differences were detected between the offspring of women diagnosed with GDM during early pregnancy vs. those diagnosed with GDM during their second trimester.

Second, when offspring were stratified according to timing of randomization (before vs. early pregnancy), a tendency towards poorer offspring metabolic health was detected in the intervention arms of both these subgroups. However, the between-group difference was significant only in the offspring of women recruited during early pregnancy (P = 0.031), and not in the offspring of women recruited before pregnancy (P = 0.28). It should be emphasized that the percentage of women recruited before pregnancy was only 27% (n = 72) of all participants included in this substudy.

Finally, our main findings were adjusted for several possible covariates. The detected between-group difference in offspring metabolic health remained significant even after adjusting for prepregnancy BMI, HOMA-IR at baseline, recruitment time point, intervention group and number of previous children. In this general linear model, only prepregnancy BMI and randomization

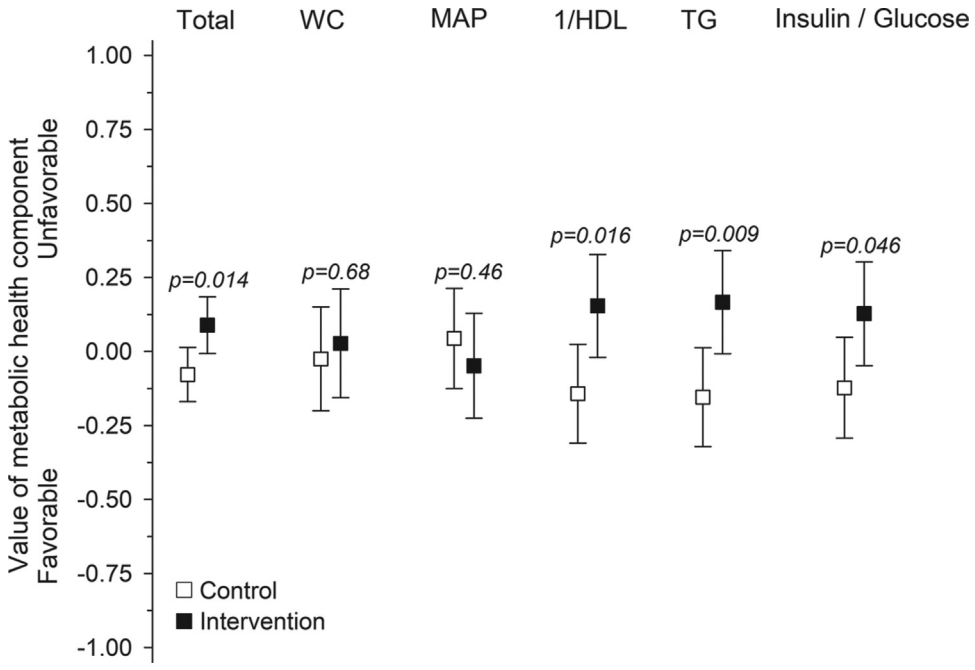

Fig. 2. Age- and gender-standardized residuals of metabolic health components in offspring at the 5-year follow-up visit by study group. Total: average of all components; WC: waist circumference; MAP: mean arterial pressure; 1/HDL: inverted high-density lipoprotein concentration; TG: triglycerides; Insulin/Glucose: fasting insulin/glucose ratio. Bars represent the confidence interval (CI).

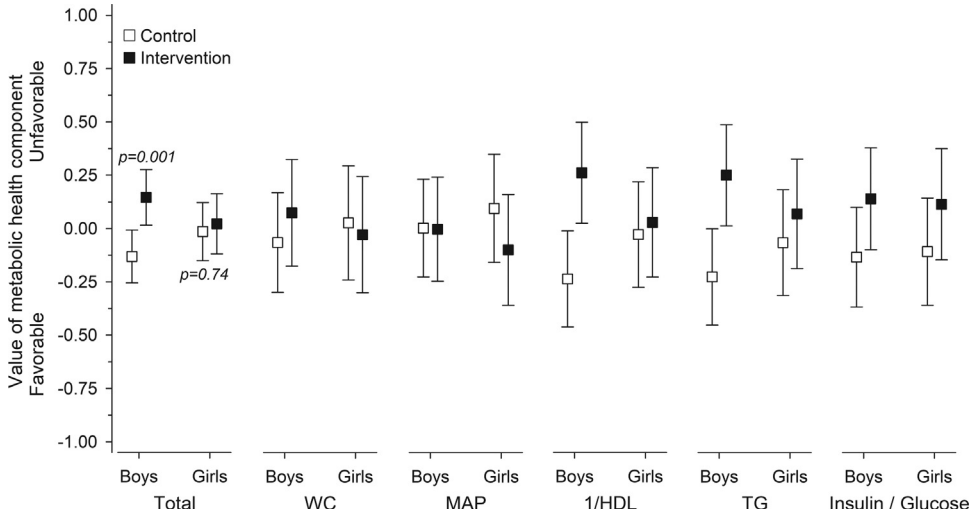

Fig. 3. Age- and gender-standardized residuals of metabolic health components in offspring at the 5-year follow-up visit by intervention group and offspring gender. Total: average of all components; WC: waist circumference; MAP: mean arterial pressure; 1/HDL: inverted high-density lipoprotein concentration; TG: triglycerides; Insulin/Glucose: fasting insulin/glucose ratio. Bars represent the confidence interval (CI).

into intervention group, in addition to intervention allocation, were associated with poorer metabolic health in the offspring.

Discussion

The aim of the present substudy was to evaluate the effect of a lifestyle intervention starting before or during early pregnancy and ending 1 year after delivery on offspring metabolic health at around 5 years of age. In fact, no positive effects of the lifestyle intervention on either metabolic health or body composition were detected in the offspring. More disturbing, given the results of this study, a lifestyle intervention applied before, during and after pregnancy might even have adverse effects on offspring metabolic health outcomes. Such adverse effects were related to offspring glucose and lipid metabolism and, more specifically, to levels of HDL cholesterol and TG. Moreover, these effects were more pronounced in boys and in the offspring of GDM pregnancies.

However, these results need to be interpreted with care, and the reasons behind them can only be speculated. The intervention was relatively modest and may not have been intensive enough to have any impact on offspring outcomes. Another explanation is the high standard of the usual antenatal care in Finland, thereby resulting in only small differences in management protocols between the intervention and control groups. Finally, variations in offspring metabolic health could depend, to a much greater extent, on genetic variances than on intrauterine conditions, as previously reported by Richmond et al. [28], who looked at the association of maternal BMI in pregnancy with offspring adiposity in childhood and adolescence.

Table 2
Offspring outcomes by study interventional or conventional care (control) group.

Characteristics	Control (n = 137)	Intervention (n = 126)	P
Offspring birth weight (g)	3663 (507)	3685 (558)	0.75
Offspring standardized birth weight (g)	0.2 (1)	0.3 (1)	0.28
Age at follow-up visit (years)	5.1 (0.54)	5.5 (0.48)	0.69
Gender of offspring:			0.90
Girls	62 [45]	58 [46]	
Boys	75 [55]	68 [54]	
Waist circumference (cm)	54.7 (4.2)	54.9 (4.4)	0.77
Mean arterial pressure (mmHg)	75 (5.8)	74 (5.7)	0.45
Fasting insulin/glucose ratio	1.0 (0.97)	1.4 (1.54)	0.05
HDL cholesterol (mmol/L)	1.6 (0.31)	1.5 (0.28)	0.01
Triglycerides (mmol/L)	0.74 (0.30)	0.87 (0.50)	0.01
Alanine aminotransferase (U/L)	19 (6.9)	19 (9.0)	0.60
hs-CRP (mg/L)	0.49 (0.83)	0.71 (1.44)	0.13
Total metabolic parameters	−0.08 (0.46)	0.09 (0.63)	0.01
Body composition	(n = 121)	(n = 106)	
Fat-free mass (kg)	17 (2.3)	17 (2.4)	0.40
Boys	17 (2.4)	17 (2.5)	0.96
Girls	17 (2.1)	16 (2.2)	0.19
Fat mass (kg)	3.6 (1.7)	3.7 (1.8)	0.77
Boys	3.2 (1.5)	3.5 (1.8)	0.29
Girls	4.2 (1.8)	3.9 (1.9)	0.43
Fat percentage (%)	17 (6.1)	17 (6.2)	0.71
Boys	15 (5.9)	16 (5.8)	0.37
Girls	19 (5.6)	19 (6.3)	0.52
BMI-for-age (Z-score)	0.66 (0.80)	0.61 (1.0)	0.67
Boys	0.63 (0.81)	0.58 (1.1)	0.75
Girls	0.69 (0.78)	0.64 (1.0)	0.78

Data are presented as means (standard deviation, SD) or as numbers [%]; HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; BMI: body mass index.

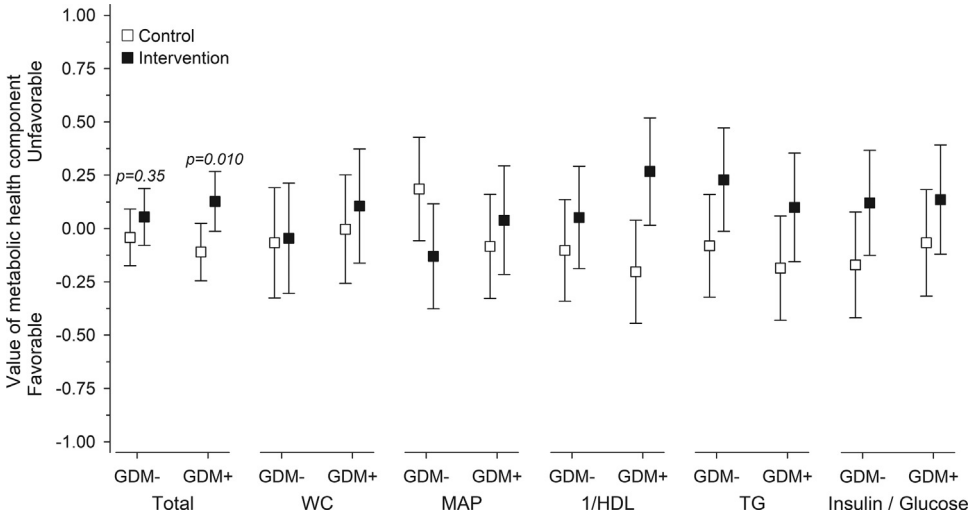

Fig. 4. Age- and gender-standardized residuals of metabolic health components in offspring at the 5-year follow-up visit by intervention group and maternal gestational diabetes mellitus (GDM) status (−: without; + with). Total: average of all components; WC: waist circumference; MAP: mean arterial pressure; 1/HDL: inverted high-density lipoprotein concentration; TG: triglycerides; Insulin/Glucose: fasting insulin/glucose ratio. Bars represent the confidence interval (CI).

In the present substudy, gender-specific effects of the lifestyle intervention were detected. This was not surprising, as previous studies have shown gender differences in fetal programming patterns, such that differences in response to various kinds of exposure during early fetal development may at least partly explain gender-related health differences in adult life [29]. However, the specific mechanisms explaining such gender differences in the developmental programming of metabolic health clearly warrant further research.

Initially, it was speculated that greater offspring body size and degrees of adiposity might explain the detected clustering of unfavourable metabolic components related to glucose regulation and lipid metabolism among the offspring of women in the intervention group. However, it appears that offspring body size, as measured by WC and BMI-for-age, and body composition, as measured by body fat mass and body fat percentage, were unaffected by the intervention.

Another possible explanation could be related to offspring liver metabolism, as previous studies have revealed that impaired glucose metabolism and dyslipidaemia in childhood are comorbidities of paediatric non-alcoholic fatty liver disease (NAFLD), a condition currently growing in incidence [30]. Nevertheless, as liver biopsy, the gold standard for diagnosing NAFLD, is neither feasibly nor ethically performed in healthy children, levels of ALT are commonly used as a proxy measure. Yet, in this substudy, analyses of ALT and hs-CRP did not add to clarification of the underlying pathological mechanisms of our findings.

Offspring exposed to GDM in utero display higher rates of overweight or obesity [31,32], impaired glucose metabolism [33], type 2 diabetes [34], hypertension [35] and MetS [36,37] later in life. In our substudy, however, GDM could not explain the differences in offspring metabolic health between groups as a whole. In our study population, a very small percentage of women had severe GDM, as reflected by the low rate of medical treatment (data not shown). In addition, participants with GDM were well monitored in both study groups, thereby minimizing the adverse effects of GDM on offspring. Interestingly, aggravation of the unfavourable effects of the intervention was detected among the offspring of women diagnosed with GDM, although the timing of GDM diagnosis did not affect our findings. Furthermore, the positive association of maternal prepregnancy BMI with poorer offspring metabolic health was anticipated and in line with previous studies [38,39].

Study limitations

One limitation of our substudy was the high rate of those lost to follow-up, potentially making conclusions on the long-term effects of GDM prevention on offspring health less reliable. However, our dropout rate was no higher than the rates (20–65%) observed in previous similar trials with long-term follow-ups of offspring [9]. In our present study, 55% of the eligible mother–child dyads attended the 5-year follow-up visit.

Analyses of the baseline data for mothers in the intervention group whose children were lost to follow-up revealed a lower mean age and smaller percentage enrolled before pregnancy compared with women whose offspring attended the follow-up. Likewise, in the control group, there was a difference in HDL concentration between mothers of attenders and mothers of non-attenders. These differences may have influenced our results, as maternal cholesterol levels could act as mediators of the effects of the intervention on offspring metabolic health.

Incomplete data on offspring body composition is another limitation of our study. In addition, the offspring fasting time before blood samples were drawn was self-reported, and even though most participants reported a 4-h fast, there was nonetheless a variance of 2–4 h. Furthermore, it would be of considerable interest to investigate the physical-activity levels and dietary patterns of offspring at the 5-year follow-up time point, as these are possible mediators of our results and could serve as secondary outcomes. Indeed, our plan is to present these data in future.

Unfortunately, the power of our study was insufficient for analyses of differences in offspring outcomes according to intervention starting point. According to previous studies of fetal programming, the timing of events is important, with the periconceptional period being the most vulnerable [40]. Thus, it would be of major interest to assess whether an intervention starting well before pregnancy would have different effects on offspring parameters compared with starting at the beginning of pregnancy.

Conclusion

The lifestyle intervention aimed at reducing diagnoses of GDM was not associated with favourable metabolic parameters of the offspring at the 5-year follow-up. On the contrary, a less optimal metabolic profile was observed among the offspring of women in the intervention group. This finding was more pronounced in boys and in the offspring of women diagnosed with GDM. Thus, our present findings highlight the delicacy required to plan and execute antenatal lifestyle interventions, and also emphasize the importance of analyzing offspring follow-up data when assessing their efficacy. Nevertheless, our present results do add further knowledge to the ongoing search for means to curb the global increase in the prevalence of non-communicable diseases.

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Clinical trial registration

ClinicalTrials.gov NCT01698385 (www.clinicaltrials.com).

Disclosure of interest

The authors declare that they have no competing interest.

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